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Green and versatile Zn–Ce nanoparticle catalyst for Benzodiazepine phamacophore synthesis

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Abstract
Transition metal Zn–Ce nanoparticles were facilely synthesized and employed as an efficient catalyst for the cyclocondensation of phenylenediamines with ethyl methyl ketone to afford the corresponding 1,5-benzodiazepine derivative (3a) in 90% yield. This novel methodology was further extended to the synthesis of various substituted benzodiazepine phamacophore molecules. The desired products were obtained in good to excellent yields (75–94%) under simple, clean and environmentally benign reaction conditions.

Keywords: Phenylenediamines, ketone, cyclocondensation, Zn–Ce NPs, Benzodiazepine

Introduction

Benzodiazepines (BZDs) are a significant class of nitrogen-containing heterocyclic compounds known for their diverse biological properties [1] Specifically, 1,4-benzodiazepines as a type of sedative, hypnotic, and myorelaxant play a remarkable role in the pharmacotherapy of central nervous system (CNS) disorders [2]. Benzodiazepines are highly accessible and effective, making them an important scaffold in medicinal chemistry [3]. They exhibit a broad spectrum of pharmacological activities, especially in the treatment of CNS disorders, including anti-epileptic, anti-psychotic, anxiolytic, anti-depressive, and sedative properties (e.g., clobazam and clozapine) [4, 5]. Additionally, benzodiazepine derivatives show anti-tumor, analgesic, antimicrobial, anti-ulcer, and anticoagulant effects [5]. They also act as inhibitors of interleukin-1β converting enzyme (ICE), hepatitis C virus NS5B polymerase, HIV-1 protease and HIV-1 reverse transcriptase and function as cholecystokinin (CCK2) receptor antagonists [6–9].

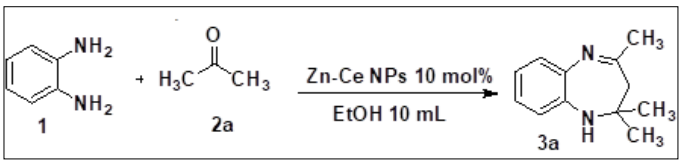
In addition, benzodiazepine derivatives are also used in industry as dyes for acrylic fibers in photography. Moreover, 1,5-Benzodiazepines have been successfully employed in the synthesis of various fused benzodiazepine derivatives, including oxadiazolo-, oxazino-, triazolo-, and furanobenzodiazepines [10].

Several catalytic systems and methodologies have been developed for the synthesis of 1,5-benzodiazepines through the condensation of o-phenylenediamine with cycloalkanone and various ketones, each offering a valuable approach for constructing heterocyclic frameworks [11]. Synthesis of benzodiazepines via catalytic performance of H-MCM-22[12], Synthesis of benzodiazepines via catalytic performance of p-toluene sulfonic acid [13], Gold catalyzed biphenyl)$Cy_2PAuNTf_2$ trisubstituted-1,5-benzodiazepines [14], Synthesis of benzodiazepines using MIL/$KrSO_3H$ as catalyst [15], $Cd(NO_2)_3$ catalysed synthesis of 1, 5-benzodiazepines [16], $Zn(OTf)_2$ catalysed Synthesis of 1,5-benzodiazepines [17] SiO_2-Pr-SO_3H catalysed [18], $PhB(OH)_2$ catalysed synthesis of 1,5-benzodiazepines [19].

Due to the broad pharmacological importance of 1,5-benzodiazepines, significant attention has been devoted to their synthesis. Literature reports indicate that various synthetic strategies for constructing this ring system involve the condensation of o-phenylenediamine (OPD) with α,β-unsaturated carbonyl compounds, β-haloketones or ketones, often in the presence of nanocatalyst to establish environmentally friendly and green protocols.

Result and Discussion

In the current strategy, the synthesis of 1,5-benzodiazepines derivatives was carried out by reacting o-phenylenediamine OPD**1** (0.001 mol) with substituted ketones **2a** (0.002 mol) in the presence of Zn–Ce NPs as a nanocatalyst, was stirred at room temperature for 2.5 h afforded 1,5-benzodiazepines (**3a**) very good yield with high purity.



Scheme: 1

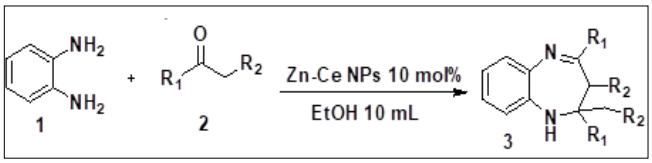
Firstly, our investigation was directed toward identifying the most suitable solvent for the synthesis of the target benzodiazepine molecule. A variety of commonly used organic solvents were evaluated in order to determine their impact on reaction efficiency and product yield. Among the solvents tested, ethanol was found to be the most effective, providing an excellent medium for the cyclocondensation reaction due to its appropriate polarity, easy availability, and environmentally benign nature. The reaction proceeded smoothly in ethanol, resulting in a cleaner product profile and higher yield compared to the other solvents examined. Therefore, ethanol was selected as the optimal solvent for subsequent experiments.

Optimization of Catalyst Amount

To determine the optimal loading of Zn–Ce nanoparticles, the reaction was performed using varying catalyst amounts. The efficiency and yield increased progressively with an increase in catalyst loading up to 10 mol%, which was identified as the optimal quantity. At this level, excellent conversion and high product yields were achieved within a shorter reaction time. Further increase beyond 10 mol% did

not lead to any significant improvement in yield, indicating that higher catalyst amounts are unnecessary. Thus, 10 mol% Zn–Ce nanocatalysts was selected as the most effective dosage for subsequent reactions.

It was observed that 10 mol% Zn–Ce nanocatalysts provided the most efficient conversion and the highest yields. Interestingly, cyclic ketones such as cyclohexanone also participated smoothly in the reaction, delivering fused-ring 1,5-benzodiazepines in excellent yields, comparable to those obtained with acyclic ketones. However, ketones containing electron-withdrawing groups showed a noticeable decrease in product yields **(75-94%).** All products were characterized by spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR and Mass) match with reported data [11, 14, 17].



Scheme 2: Synthesis of Benzodiazepine Derivatives

Table 1: Study of cyclocondensation with substituted ketones

Entry	Compound	Ketone		Time (Hrs)	Yield.
		R^1	R^2		
1	3a	CH_3	H	2.5	81
2	3b	CH_3	CH_3	3	94
3	3c	Ph	H	3	88
4	3d	4-MePh	H	2	91
5	3e	3-NO_2Ph	H	3.5	75
6	3f	Cyclohexanone		4	90
7	3g	Cyclopentanone		3	87

[a]**Reaction Condition:** i) o-phenylenediamine (0.001 mol), ketones (0.002, mol), Zn-Ce NPs (10 mol%) EtOH 10 mL, at rt; [b] yield of product after chromatographic purification.

Experimental Section

Materials and Methods

All reactions were performed in dry solvents unless stated otherwise and monitored by TLC on silica gel 60 F254 plates (Merck) using UV light or staining reagents. Products were characterized by ^{1}H NMR, ^{13}C NMR, IR, and Mass. NMR (Varian Mercury 300 MHz), IR (Shimadzu FTIR-8400), and Mass spectrometry (70 eV). Melting points are uncorrected. Column chromatography was carried out on silica gel (100–200 mesh) using ethyl acetate/hexane as eluents.

Experimental

In a round bottom flask was charged with a mixture of Zn-Ce NPs (10 mol%) in dry Ethanol (10 mL) was stirred at room temperature for 10 min, add to it phenyldiamine (0.001 mmol) reaction mixture can be stirred additional 10 min and finally add ethyl methyl ketone (0.002 mL) and reaction stirred until starting material was totally consumed. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of reaction, filtered the reaction mixture by filter paper, collect organic layer and the solvent was removed by evaporation. The reaction mixture was diluted with ethyl acetate (20 mL) Evaporate solvent to dryness, and purified by silica gel column chromatography with hexane/EtOAc (80:20%) to afford desired product yield 90%.

2,2,4-Trimethyl-2,3-dihydro-1H-1,5-benzodiazepine

3a[14]: as colourless solid. Yield: 90%, m.p 138-141. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.01-7.06 (m, 1H), 6.87-6.89 (m, 2H), 6.59-6.84 (m, 1H), 2.94 (s, 1H), 2.24 (s, 3H), 2.09 (s, 2H), 1.20 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 140.3, 137.7, 126.4, 125.2, 121.6, 121.4, 68.0, 44.7, 30.1, 29.5 ppm. IR (KBr) 3350, 1638, 1610, 1454, 1259, 1198, 1113 cm^{-1}. (ESI): *m/z* calcd for $C_{12}H_{16}N_2$ $[M + H]^+$ 189.0451: found; 189.0458.

Conclusion

In conclusion, we have developed a simple and efficient method for synthesizing 1,5-benzodiazepine derivatives via the cyclocondensation of o-phenylenediamine with various ketones, using Zn-Ce NPs as a catalyst in Ethanol at room temp. The protocol offers easy operation, our protocol is an efficient and green method with several advantage mild reaction conditions, simple work-up procedure, and good to excellent yields across a wide range of ketones, inexpensive reagents, and separation of catalyst with simple filtration.

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Conflicts of Interest

There are no conflicts Interest to declare.

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